

REMARKS

Status of the Claims

In this paper, claims 1 and 7-9 have been cancelled without prejudice or disclaimer. No new matter has been added.

Now pending are claims 13, 14, 16, and 17.

Applicants note with appreciation the Examiner's withdrawal of the prior rejection under 35 U.S.C. §112, second paragraph. Applicants request reconsideration of the remaining rejections in view of the remarks herein.

Rejections under 35 U.S.C. §103(a)

(a) In the Office Action, claims 1 and 7-9 were rejected as unpatentable over Ledger et al. (U.S. Patent No. 5,120,545) in view of Inagi et al. (U.S. Patent No. 5,577,028). As noted above, claims 1 and 7-9 have been cancelled, so the rejection of these claims is moot. Withdrawal of the rejection is therefore proper and is requested.

(b) In the Office Action, claims 1, 7-9, 13, 14, 16 and 17 stand rejected as unpatentable over Kawaji et al. (U.S. Patent No. 6,261,121) in view of Arellano (European Journal of Pharmaceutical Sciences) and further in view of Porter et al. (U.S. Patent No. 5,968,533). As noted above, claims 1 and 7-9 have been cancelled, so the rejection of those claims is moot. As to the remaining claims, this rejection is traversed.

According to the Office Action, Kawaji "[teaches] oil patches containing diclofenac sodium and fatty acids which are combined in an adhesive." Office Action at page 9. The Office Action concedes that Kawaji does not disclose the use of ammonium chloride in the patch. However, the Office Action states that Arellano teaches "the inclusion of propylene glycol and isopropyl myristate on the penetration of diclofenac sodium . . . It is taught that these agents are penetration enhancer [sic] in the topical formulations of drugs." The Office Action states that Porter

is directed to adhesive materials utilizing a patch to deliver active agents . . . It is taught that utilization of certain ingredients in the patches can increase the release rates and/or absorption rates of the active ingredients(i.e. they are penetration enhancers). Disclosed additives which increase the release rate include ethylene glycol, polyethylene glycols and ammonium chloride.

The Office Action concludes, "It would have been obvious to one of ordinary skill in the art to have combined the teachings of Kawaji et al., Arellano et al., and Porter et al. and utilize ammonium chloride in the invention of Kawaji et al." Office Action at page 10. Applicants do not agree.

As Applicants understand the reference, Kawaji discloses the use of oily patches for external use containing sodium diclofenac, isostearic acid, and a fatty acid. According to Kawaji, combining a fatty acid with diclofenac sodium to produce the free acid of diclofenac (in order to improve transdermal absorption of diclofenac) results in simultaneous production of the sodium salt of the fatty acid, which can cause skin irritation (Kawaji, Column 2, lines 24-31). Kawaji also teaches the addition of isostearic acid for prevention of skin irritation (Kawaji, Column 2, lines 24-31). Kawaji does not teach or suggest the use of sodium diclofenac with an acid addition salt of an amine (including ammonium chloride), nor does Kawaji teach or suggest that low skin irritation and improved percutaneous absorbability can be achieved through the use of ammonium chloride, as recited by the pending claims.

As Applicants understand the reference, Arellano describes aqueous preparations of diclofenac and propylene glycol and/or isopropyl myristate. Thus, Arellano describes percutaneous absorbability of aqueous preparations. Applicants respectfully submit that it would not be obvious to combine the oily preparations of Kawaji with the aqueous preparations of Arellano.

Further, Arellano discloses that when cellulose nitrate membrane was used as barrier, penetration rate (cumulative amount) of diclofenac was increased due to the influence of propylene glycol (PG) (see, e.g., p. 131, Fig. 3 of Arellano). However, when abdominal rat skin was used, the penetration rate (cumulative amount) was decreased (see, e.g., p.132, Fig. 4 and p.132, left column, last

paragraph to p.133, left column, line 4, of Arellano). The action of PG as a cosolvent has been further investigated in Arellano, and Arellano reports that the penetration rate (cumulative amount) was increased according to the addition of isopropyl myristate (IPM) (see, e.g., Fig. 5, p. 133 of Arellano). More specifically, Arellano discloses that when animal skin was used as a barrier, PG itself did not promote the penetration of diclofenac sodium, although it exhibited cosolvent activity.

Thus, contrary to statements in the Office Action, one of skill in the art would not regard PG as a penetration enhancer interchangeable with ammonium chloride based on the teachings of the cited references. Moreover, PG is a liquid that can be used as a solvent; however, ammonium chloride is a solid that cannot be used as solvent. One of ordinary skill in the art would not expect ammonium chloride to have cosolvent activity.

As Applicants understand the reference, Porter describes polyethylene glycols or ammonium chloride as water-soluble additives which enhance percutaneous absorbability (see, e.g., Col. 5, lines 24-27 of Porter) in skin care transdermal delivery devices (patches) comprising a water-soluble antioxidant such as vitamin C and a moisturizer such as hyaluronic acid (col. 4, lines 7-16). Porter describes only aqueous preparations and percutaneous absorbability thereof. Porter mentions ammonium chloride as increasing release rate, but only for enhancement of release of a water-soluble antioxidant such as vitamin C and moisturizer such as hyaluronic acid in aqueous preparations. Porter is completely silent regarding the percutaneous absorbability of salt-form acidic drugs such as diclofenac sodium in a non-aqueous system.

Even if Porter suggests that propylene glycol and ammonium chloride are functionally equivalent as percutaneous absorbability enhancers in skin care transdermal delivery devices (patches) (which Applicants do not concede), Applicants point out that, as discussed above, Arellano discloses that PG itself does not promote the penetration of sodium diclofenac when animal skin is used as barrier. Therefore, one of ordinary skill in the art would not expect, based on the

teachings of the cited references, that ammonium chloride could enhance percutaneous absorbability of sodium diclofenac in a non-aqueous patch, if indeed propylene glycol and ammonium chloride are functionally equivalent. The cosolvent activity of PG and ammonium chloride apparently differ in their properties.

Accordingly, Applicants contend that Arellano and Porter show that PG and ammonium chloride should not be considered as equivalents as far as the percutaneous absorbability of salt forms of acidic drugs, such as sodium diclofenac, are concerned. If it is assumed, *arguendo*, that PG and ammonium chloride would act equivalently with respect to the percutaneous absorbability of salt-form acidic drugs such as sodium diclofenac, Arellano would teach that neither PG nor ammonium chloride enhances percutaneous absorbability of diclofenac sodium with respect to animal skin. To this extent, Arellano can be seen to teach away from the combination of references cited in the Office Action.

As noted above, the Office Action concedes that Kawaji does not teach or suggest the use of ammonium chloride to improve the percutaneous absorbability of the oily preparation of Kawaji. Neither the Arellano reference nor the Porter reference, whether considered separately or in combination, can bridge the gap between the deficient teachings of Kawaji and the subject matter of the pending claims. None of Kawaji, Arellano, or Porter (alone or in combination) render obvious the use of ammonium chloride in a non-aqueous patch as claimed.

Still further, one of ordinary skill in the art would not be motivated to combine the disclosures of Kawaji (relating to oily preparations) with the disclosures of Arellano and/or Porter (both relating to aqueous preparations). Moreover, one of skill in the art would not have the requisite reasonable expectation of success in making such a combination. Applicants respectfully submit that the presently-claimed subject matter is not and cannot be rendered obvious by any of Kawaji, Arellano, and Porter, whether taken alone or in any combination.

Finally, and as discussed in a previous response (filed November 23, 2008), while Applicants contend that the Office Action has failed to make out a *prima facie* case of obviousness of the pending claims, Applicants submit that any *prima facie*

case of obviousness is rebutted by evidence of the unexpected properties of the claimed percutaneous preparations. As seen from the Examples provided in the specification, preparations including ammonium chloride in addition to sodium diclofenac have enhanced skin permeability compared to preparations having no ammonium chloride. See, e.g., Example 4 (about 7-fold increase in skin permeability rate with ammonium chloride compared to Comparative Example 4 without ammonium chloride) and Example 19 (about 4.8-fold increase in skin permeability rate with ammonium chloride compared to Comparative Example 19 without ammonium chloride). Applicants submit that such unexpectedly superior properties are not and cannot be obvious, and that the presently-claimed methods are not obvious in view of the cited references. The Office Action appears to give no weight to the evidence of unexpected results, stating that “[t]he prior art teaches compositions comprising ammonium chloride.” Applicants respectfully contend that, as discussed above, none of the references cited with respect to the pending claims discloses a non-aqueous composition comprising ammonium chloride. In any case, Applicants submit that a comparison of compositions with and without ammonium chloride (as discussed above) is relevant and should be considered by the Office.

Reconsideration and withdrawal of the rejections is proper and such action is requested.

Double Patenting Rejections

In the Office Action, claims 1, 7-9, 13, 14, 16 and 17 stand provisionally rejected on the ground of obviousness-type double patenting over certain claims of co-pending application no. 10/479,072. As noted above, claims 1 and 7-9 have been cancelled, so the rejection of these claims is moot. As to the remaining claims, Applicants point out that the present application has an earlier effective filing date than the ‘072 application.

In the Office Action, claims 1, 7-9, 13, 14, 16 and 17 stand provisionally rejected on the ground of obviousness-type double patenting over certain claims of co-pending application no. 10/549,184 in view of Arellano and Porter. As noted

above, claims 1 and 7-9 have been cancelled, so the rejection of these claims is moot. As to the remaining claims, Applicants point out that the present application has an earlier effective filing date than the '184 application. In addition, the Office Action concedes that the '184 claims do not disclose the addition of ammonium chloride, but states that Arellano and Porter cure this deficiency in the disclosure of the claims of the '184 application. However, as discussed above with respect to the Kawaji reference (which similarly lacked a teaching of the use of ammonium chloride), neither Arellano nor Porter, separately or in combination, would motivate one of skill in the art to modify the claims of the '184 application to arrive at the presently-claimed subject matter. Neither Arellano nor Porter, separately or in combination, would provide a reasonable expectation of success in making such a modification. Applicants respectfully contend that the presently-pending claims are not rendered obvious by the '184 claims in view of either Arellano or Porter.

In the Office Action, claims 1, 7-9, 13, 14, 16 and 17 stand provisionally rejected on the ground of obviousness-type double patenting over certain claims of co-pending application no. 10/548,739 in view of Arellano and Porter. As noted above, claims 1 and 7-9 have been cancelled, so the rejection of these claims is moot. As to the remaining claims, Applicants point out that the present application has an earlier effective filing date than the '739 application. In addition, the Office Action concedes that the '739 claims do not disclose the addition of ammonium chloride, but states that Arellano and Porter cure this deficiency in the disclosure of the claims of the '739 application. However, as discussed above with respect to the Kawaji reference (which similarly lacked a teaching of the use of ammonium chloride), neither Arellano nor Porter, separately or in combination, would motivate one of skill in the art to modify the claims of the '739 application to arrive at the presently-claimed subject matter. Neither Arellano nor Porter, separately or in combination, would provide a reasonable expectation of success in making such a modification. Applicants respectfully contend that the presently-pending claims are not rendered obvious by the '739 claims in view of either Arellano or Porter.

In the Office Action, claims 1, 7-9, 13, 14, 16 and 17 stand provisionally rejected on the ground of obviousness-type double patenting over certain claims of co-pending application no. 11/596,605 in view of Arellano and Porter. As noted above, claims 1 and 7-9 have been cancelled, so the rejection of these claims is moot. As to the remaining claims, Applicants point out that the present application has an earlier effective filing date than the '605 application. In addition, the Office Action concedes that the '605 claims do not disclose the addition of ammonium chloride, but states that Arellano and Porter cure this deficiency in the disclosure of the claims of the '605 application. However, as discussed above with respect to the Kawaji reference (which similarly lacked a teaching of the use of ammonium chloride), neither Arellano nor Porter, separately or in combination, would motivate one of skill in the art to modify the claims of the '605 application to arrive at the presently-claimed subject matter. Neither Arellano nor Porter, separately or in combination, would provide a reasonable expectation of success in making such a modification. Applicants respectfully contend that the presently-pending claims are not rendered obvious by the '605 claims in view of either Arellano or Porter.

In the Office Action, claims 1, 7-9, 13, 14, 16 and 17 stand provisionally rejected on the ground of obviousness-type double patenting over certain claims of co-pending application no. 10/258,022 in view of Arellano and Porter. As noted above, claims 1 and 7-9 have been cancelled, so the rejection of these claims is moot. As to the remaining claims, Applicants point out that the present application has an earlier effective filing date than the '022 application. In addition, the Office Action concedes that the '022 claims do not disclose the addition of ammonium chloride, but states that Arellano and Porter cure this deficiency in the disclosure of the claims of the '022 application. However, as discussed above with respect to the Kawaji reference (which similarly lacked a teaching of the use of ammonium chloride), neither Arellano nor Porter, separately or in combination, would motivate one of skill in the art to modify the claims of the '022 application to arrive at the presently-claimed subject matter. Neither Arellano nor Porter, separately or in combination, would provide a reasonable expectation of success in making such a

modification. Applicants respectfully contend that the presently-pending claims are not rendered obvious by the '022 claims in view of either Arellano or Porter.

Without agreeing with any of the double patenting rejections, Applicants point out that each of the rejections is provisional, and that the corresponding claims have not yet been patented. Applicants respectfully request that any provisional double patenting rejections be deferred until the present application is otherwise in condition for allowance.

Reconsideration and withdrawal of the rejections is proper and the same is requested.

Conclusion

For at least the foregoing reasons, Applicants request reconsideration of the application. Early and favorable action is requested.

Applicants request any extension of time necessary for consideration of this response. If for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge Deposit Account No. **04-1105**, under Reference No. 56769 (71526), Customer No. 21874.

Respectfully submitted,

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